

PATENT COOPERATION TREATY

PCT

REC'D 12 SEP 2005

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY PCT

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference L 1792 PCT	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/US2004/033698	International filing date (day/month/year) 14.10.2004	Priority date (day/month/year) 16.10.2003	
International Patent Classification (IPC) or national classification and IPC C07C279/28, C07C237/22, A61K31/17, A61K31/165, A61P25/04			
Applicant FERRING B.V.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau)</i> a total of sheets, as follows:</p> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <p>b. <input type="checkbox"/> <i>(sent to the International Bureau only)</i> a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application 			
Date of submission of the demand 17.05.2005	Date of completion of this report 09.09.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seufert, G Telephone No. +49 89 2399- 		

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/033698

Box No. I Basis of the report

- With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - international search (under Rules 12.3 and 23.1(b))
 - publication of the international application (under Rule 12.4)
 - international preliminary examination (under Rules 55.2 and/or 55.3)
 - With regard to the elements* of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-21 as originally filed

Claims, Numbers

1-17 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. The amendments have resulted in the cancellation of:

 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

4. This report has been established as if (some of) the ~~amendments~~ annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/033698

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 17 for industrial applicability
 - because:
 - the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (specify):
see separate sheet
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos. 1-8(part), 10-12(part), 14-17(part)
 - the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard
the computer readable form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard
- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/033698

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9, 13
	No:	Claims	1-8, 10-12, 14-17
Inventive step (IS)	Yes:	Claims	1-8, 10-17
	No:	Claims	9
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.
PCT/US2004/033698

Reference is made to the following documents:

- D1 DE 33 29 628 A1
- D2 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 8702792
- D3 DE 20 05 326 A1
- D4 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 2808453
- D5 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 2993980
- D6 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 7033473
- D7 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 4450540, 4435773
- D8 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 7218655, 7218660
- D9 US-A-5 516 795
- D10 US-A-2 447 587
- D11 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database accession no. BRN 2669014
- D12 J. ORG. CHEM., vol. 58, no. 6, 1993, pages 1425-1433

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds of formula (I) whereby Z has the values of claim 6. Despite this limitation the search still revealed too many relevant documents for the issue of novelty. Therefore the search has been further restricted to compounds of formula (I) whereby Z is equal to $(CH_2)_3$ or to 1,2-cycloalkylene, which includes all explicitly mentioned compounds.

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to compounds of the general formula (I) (claim 1), pharmaceutical compositions comprising them (claim 15) and their use in the treatment of pain (claims 16 and 17).

Compounds falling within the scope of claim 1 and the dependent claims 2-8 and 10-12 are anticipated by the documents D1-D12 (see the cited passages in the International search report). Claims 1-8 and 10-12 are therefore not considered to meet the requirement of Art. 33(2) PCT.

Document D1, furthermore, discloses a pharmaceutical use for compounds according to claim 1, pharmaceutical compositions comprising them and their use as analgetica (see D1, abstract; claims 18-20; page 67, line 13). The subject-matter of claims 14-17

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.
PCT/US2004/033698

is therefore not considered to be novel contrary to the requirement of Art. 33(2) PCT. It should be noted that D1 not only anticipates explicit compounds falling within the scope of formula (I), but the compounds according to D1 overlap with the presently claimed compounds. No novel teaching is present for this overlapping area (Art. 33(2) PCT).

The explicit compounds mentioned in claims 9 and 13 of the present application appear to meet the requirement of Art. 33(2) PCT, because none of the available prior art documents discloses such compounds.

Inventive step

The problem to be solved by the present invention was the provision of further compounds for the treatment of pain.

With regard to D1, which already discloses compounds of formula (I) with X=CHR¹ for the same use, no inventive step can be acknowledged for the subject-matter of claims 1, 10-13 and 14-17 (amide derivatives).

With regard to the urea derivatives, i.e. compounds of claim 1 with X=NR¹ (claims 1-9, 14-17), no inventive step can be acknowledged for the following reasons:

To be considered inventive the technical problem has to be solved over basically the whole scope of the claims. However, claim 1 encompasses a large amount of compounds, while only a very small part is supported by the description (i.e. compounds of formula (I) with Z equal to (CH₂)₃ or to 1,2-cycloalkylene). Especially the biological data are insufficient to demonstrate whether the problem is actually solved over basically the whole scope of the claims. Without such data no inventive step can be acknowledged.

This objection, in addition to the aforementioned objection, is also valid for the amide derivatives.

The subject-matter of claim 9 appears to meet the requirement of Art. 33(3) PCT.

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.
PCT/US2004/033698

It should be noted that with regard to D1 the present application appears to lacks unity of invention.

Industrial applicability

For the assessment of the present claim 17 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

There are no objections against the industrial applicability of the subject-matter of claims 1-16.

Further remarks:

The claims are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: The claims encompass a large amount of compounds, while only a very small part is supported by the description (explicit examples) Furthermore, the biological data are not sufficient to support the fact that all compounds falling within the formula (I) have the desired activity.

Claim 12 is unclear (Art. 6 PCT). It is especially unclear whether it has to be understood that Y, Z, Ar, R₂ R₃ and R₆ should assume the values defined in claims 4-8 at the same time or independently (equivalent to separate claims similar to claims 4-8).

It has been understood that the variable Ar can be substituted by the substituents (b) to (l) (see description page 4, line 10-11). This is not reflected in claim 1, where no substitution

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.
PCT/US2004/033698

is mentioned for Ar. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

It should be noted that a possible substitution on Ar has been taken into account both in the search and for the purpose of the present opinion.

A bicyclic heteroaromatic ring system generally does not include a ring system whereby one of the rings is a phenyl or a five- or six-membered heteroaromatic ring fused with a heterocycl, whereby the heterocycl is saturated or partially saturated (see application page 4, line 31 - page 5, line 17). This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT. Specific definitions should be present in the claims.

A similar objection is valid with regard to the definition "C₁₋₆ straight alkyl" in the claims. This definition does not include isopropyl or 2-n-butyl groups (see application page 5, lines 18-21).

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.